# 4-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-8-(phenylmethoxy)-2-naphthalenecarboxylic Acid: A High Affinity, Competitive, Orally Active Leukotriene $B_4$ Receptor Antagonist

Fu-Chih Huang,*,† Wan-Kit Chan,† James D. Warus,† Mathew M. Morrissette,† Kevin J. Moriarty,† Michael N. Chang,† Jeffrey J. Travis,‡ Laurie S. Mitchell,‡ George W. Nuss,‡ and Charles A. Sutherland‡

*Departments of Medicinal Chemistry and General Pharmacology*
*Rhone-Poulenc Rorer Central Research*
*500 Arcola Road*
*Collegeville, Pennsylvania 19426*

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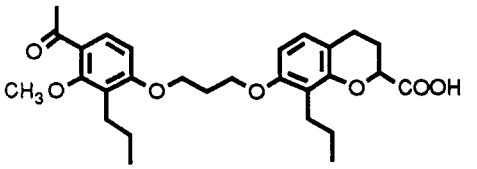
Leukotriene $B_4$ is a potent activator for polymorphonuclear (PMN) leukocytes.[1] It causes increased chemotactic and chemokinetic migration, aggregation, degranulation, lysosomal enzymes release, and free radical release. Because of these biological activities, $LTB_4$ may play an important role in inflammatory diseases in which elevated levels of $LTB_4$ have been detected, such as inflammatory bowel disease, rheumatoid arthritis, and psoriasis. The effects of $LTB_4$ are mediated through high- and low-affinity receptors on the surface of leukocytes. Since many receptor antagonists of other potent mediators have already demonstrated therapeutic value in man, the search for $LTB_4$ receptor antagonists represents a rational therapeutic approach to inflammatory diseases. In this communication, we report the discovery of a potent new $LTB_4$ antagonist.

Several $LTB_4$ receptor antagonists with a variety of biological activities have been reported in the literature. For example, SC-41930 (1), a well-studied $LTB_4$ antagonist with multiple biological activities, exhibits only moderate binding affinity ($IC_{50}$ = 300 nM) to human neutrophils.[2] Upjohn reported a series of $LTB_4$ structure-based antagonists with $IC_{50}$ values ranging from 80 to 400 nM, but most of the compounds appear to exhibit mixed agonist/antagonist activity.[3] Recently, Eli Lilly has reported LY 223982 (2) as a potent $LTB_4$ antagonist with an $IC_{50}$ of 12 nM against human PMN $LTB_4$ receptors.[4] ONO-LB-457 (3), which has a similar but slightly modified structure, is also a high-affinity $LTB_4$ antagonist.[5] Interestingly, structure–activity relationship studies reveal that both of the acidic groups are required in the chemical series related to both 2 and 3 for high binding affinity. This is in contrast to the structural features of the natural ligand. We report here that RG 14893, 4-[2-[methyl(2-phenethyl)amino]-2-oxoethyl]-8-(phenylmethoxy)-2-naphthalenecarboxylic acid (4), a compound currently being evaluated for clinical development, is a novel, high-affinity competitive $LTB_4$ receptor antagonist with oral activity.

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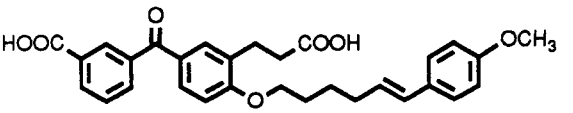


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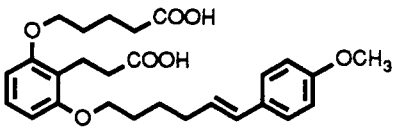


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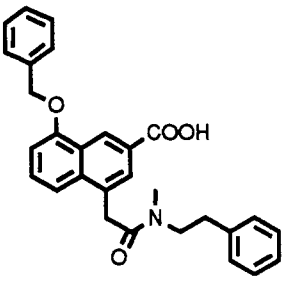


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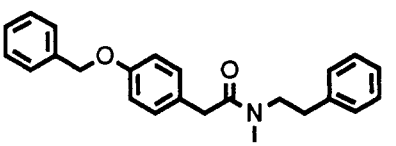


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The synthesis of 4 resulted from our initial observation that a simple phenacetamide derivative 5 displayed

† Department of Medicinal Chemistry.
‡ Department of General Pharmacology.

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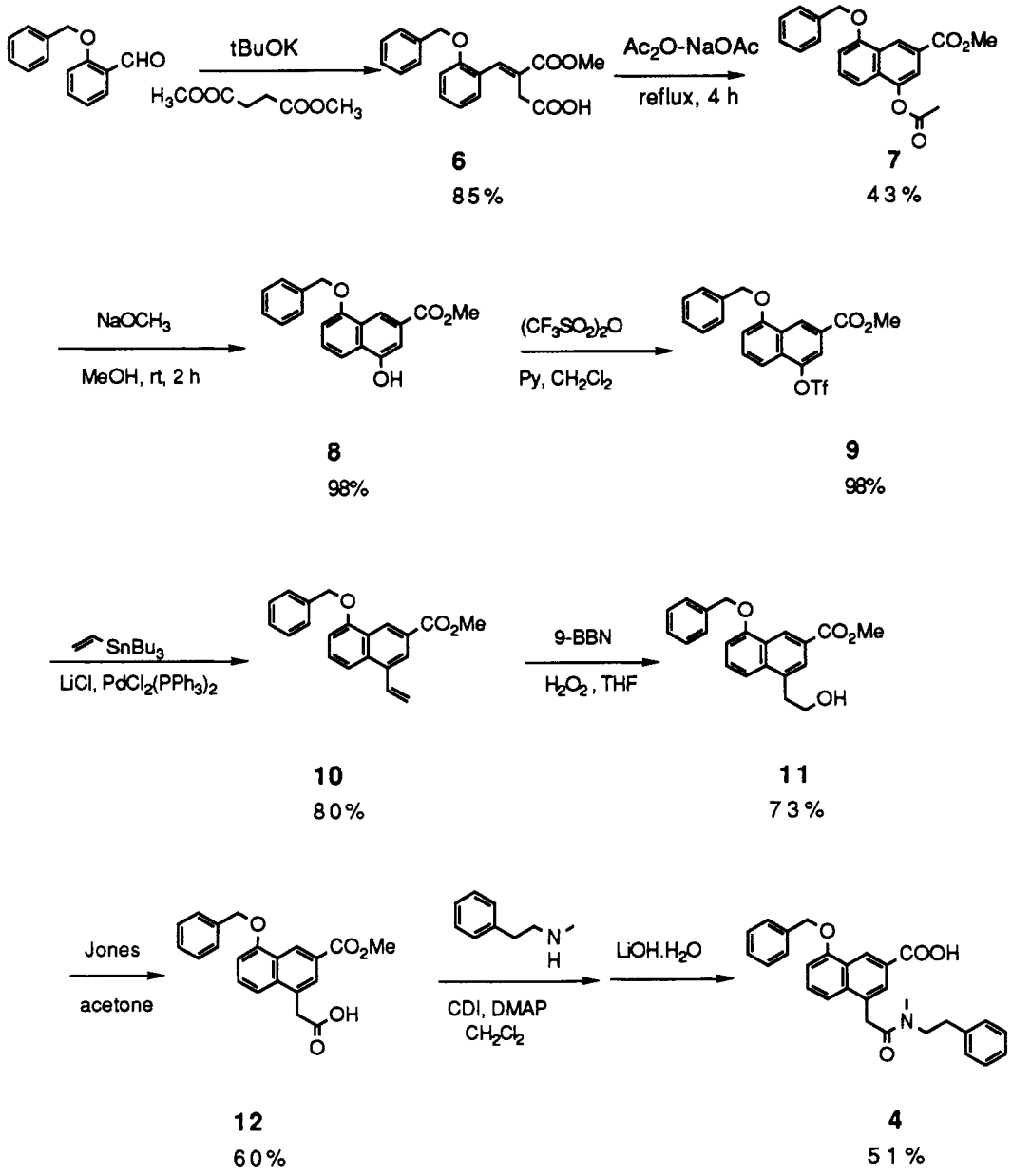
**Scheme I**




moderate binding affinity with an $IC_{50}$ of 4.7 $\mu$M in a human PMN leukocyte $LTB_4$ receptor binding assay. A series of structure–activity relationship led to the synthesis of **4** (Scheme I). These studies include (a) establishing *N*-methyl-*N*-phenethylacetamide as key binding ligand to $LTB_4$ receptor, (b) addition of an acidic functional group to improve binding affinity (based on the chemical attributes of the $LTB_4$ molecule), (c) replacing the center phenyl ring with other aromatic moieties, and (d) optimizing the geometrical relationship of the functional groups. The Stobbe condensation of *o*-(benzyloxy)-benzaldehyde with dimethyl succinate gave **6** as mixtures of *E* and *Z* isomers which were used directly in the next step. Cyclization of **6** with $Ac_2O$–NaOAc provided the naphthalene derivative **7**.[6] After methanolysis, the resulting phenol **8** was converted to the triflate **9**. Palladium-catalyzed vinylation of **9** with vinyltributyltin gave **10**.[7] Hydroboration of **10** with 9-BBN followed by oxidation of **11** with Jones reagent provided **12**, which upon coupling with *N*-methylphenethylamine followed by base hydrolysis gave **4**[8] as a crystalline solid, mp 179–181 °C.

Initially, radioligand receptor binding assays using guinea pig (GP) spleen cell membrane $LTB_4$ receptors were employed to determine the affinity of compounds.[9] In this assay, **4** is an extremely potent $LTB_4$ antagonist with an $IC_{50}$ of 0.36 ± 0.04 nM vs 0.5 nM ligand. Subsequent receptor binding studies reveal that **4** is also a potent inhibitor of the binding of [$^3$H]$LTB_4$ to human

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(8) $^1$H NMR (270 MHz, $CDCl_3$): $\delta$ 2.88, 2.91 (2 H, d, t), 2.98, 3.08 (3 H, d, t), 3.67 (2 H, m), 3.79, 4.12 (2 H, d, s), 5.29, 5.31 (2 H, d, s), 6.91, 6.93 (1 H, d, d), 7.12–7.54 (12 H, m), 7.82, 8.01 (1 H, d, s), 9.12, 9.14 (1 H, d, s). HR-EI-MS: *m/z* 453.1944.

(9) The guinea pig $LTB_4$ receptor binding assay is purchased as a kit from New England Nuclear Research Products (Catalog No. NED-005A).

whole cell neutrophils.[10] In this assay, 4 exhibits an $IC_{50}$ of 4.7 ± 0.8 nM ($n$ = 5) vs 0.5 nM ligand. By Scatchard analysis, 4 exhibits $K_i$s of 0.14 and 2 nM for guinea pig and human PMN $LTB_4$ receptors, respectively. In a GP PMN aggregation assay,[11] 4 inhibits 1 nM $LTB_4$-induced aggregation with an $IC_{50}$ of 0.8 nM. The inhibitory activity is dose-dependent and freely reversible. In addition, 4 exhibited no agonist activity at all concentrations evaluated in the aggregation assay. These results indicate that there is a good correlation between the binding affinity and functional antagonist activity of 4 against $LTB_4$ high-affinity receptors in guinea pigs.

The in vivo activity of 4 was evaluated in two different animal models. It has been shown that intradermal injection of $LTB_4$ induces neutrophil accumulation in the skin in animal models[12] and in man,[13] consistent with its in vitro chemotactic properties. When 4 is administered orally followed immediately by radiolabeled donor neutrophils and 1 μg of $LTB_4$ (id), it effectively inhibits the chemotaxis of $^{111}$indium-labeled PMNs to the $LTB_4$-induced wheals in guinea pigs ($ED_{50}$ = 0.14 mg/kg po).[14] The data confirmed that 4 is a potent, orally active antagonist of $LTB_4$ high-affinity receptors.

The effect of 4 on $LTB_4$-induced neutrophil functions in monkey was also studied.[15] Systemic administration of $LTB_4$ (0.3 μg/kg) to cynomolgus monkeys causes an immediate neutropenia followed by subsequent neutrophilia several minutes later. When administered intravenously at the dose of 3 mg/kg 2 min before challenge with $LTB_4$, 4, which has an $IC_{50}$ of 9 nM in the monkey neutrophil $LTB_4$ receptor binding assay, inhibits neutropenia and neutrophilia (61% and 73%, respectively) in this model.

It has been more than a decade since $LTB_4$ was reported as a potent activator for PMN leukocytes, and only a very limited number of potent $LTB_4$ receptor antagonists have been reported in the literature. The role of $LTB_4$ in various disease states also remains to be established. We report here that 4, a novel and potent $LTB_4$ antagonist both in vitro and in vivo, has been selected for further development and potential clinical evaluation and expect that it will serve as a useful agent in elucidating the pathophysiological role of $LTB_4$ in human diseases. Details of the structure–activity relationships of this new series of $LTB_4$ antagonists will be described in forthcoming publications.

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